REMARKS

This is in response to the Official Action of July 28, 2004. Reconsideration in light of the remarks set forth below is respectfully requested.

I. Specification

It is requested in the reference to the cited application on Pg. 10, lines 13, 14, be updated to indicate that it is now Patent No. 6,368,831.

II. Claim Rejections – 35 USC § 132 and § 112 ¶1

It is said in the official action that:

> The Specification only discloses egg phospholipids in the context of being a non-ionic surfactant. As such, according to the Specification the egg phospholipid would have to be non-ionic. However, as indicated previously in the prior Office Actions, in the context of an enablement rejection, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicant lists egg phospholipids as non-ionic surfactants, however, the prior art cited indicates that egg phospholipids are ionic surfactants. Applicant does not appear to show how the egg phospholipids are nonionic, as such, it appears that a skilled artisan would be required to do undue experimentation in order to make and/or use a non-ionic egg phospholipid. Since non-ionic egg phospholipids are non-enabled and Applicant does not describe the use of other forms of egg phospholipids other than non-ionic, Applicant's insertion of egg phospholipids per se constitutes new matter.

Official Action of July 28, 2004 at p. 2-3.

First, to resolve the new matter component of this rejection, the rejection under 35 U.S.C. §132, applicants have reverted to claim set previously presented to the Examiner prior to the objected-to amendment.

Second, in order to address the Examiner's ongoing objection to the use of non-ionic egg phospholipids as not enabled under 35 U.S.C. §112 ¶1, a Rule 132 Declaration of Dr. Shanker Gupta, a co-inventor of the present invention, is submitted concurrently. [Please note: the attorney docket number originally printed on page 1 of Dr. Gupta's declaration is incorrect. The undersigned has today amended the attorney docket number to correctly read 9022-30.] As is explained in Dr. Gupta's Declaration, it is known for one in the field of pharmaceutical formulation chemistry to use egg phospholipids as non-ionic surfactants. Some of the confusion regarding the use of egg phospholipids as non-ionic surfactants arises

because a phospholipid can be an ionic surfactant under some conditions, but can also be non-ionic under other conditions. This is because the phospholipid's net charge depends on pH. The egg phospholipids described in the above-captioned application were non-ionic because they were utilized as neutral molecules at physiological pH. Further, egg phospholipids have been utilized by others in the field of pharmaceutical formulation chemistry and referred to as a **nonionic** surfactant. *See* **Ex. 4 to Gupta Declaration**, Timothy J. Young, Keith P. Johnston, Gary W. Pace, and Awadhesh K. Mishra. "Phospholipid-Stabilized Nanoparticles of Cyclosporine A by Rapid Expansion from Supercritical to Aqueous Solution." AAPS PharmSciTech , 5 (1) Article 11 (http://www.aapharmscitech.org), 2003 (describing solution as including nonionic surfactants (p. 1) and listing Lipoid E80 as one of the surfactants used (p. 5)).

Because (a) egg phospholipids are common materials; (b) the constituents of egg phospholipids are known to contain a quaternary ammonium group; (c) such phospholipids containing a quaternary ammonium group are neutral and physiological pH; and (d) because other skilled persons in the field have described egg phospholipids as nonionic surfactants, persons skilled in the art would easily be able to practice my invention utilizing egg phospholipids as nonionic surfactants.

III. Claim Rejections – 35 USC § 103

The official action states that "Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lopez-Berenstein et al.** (US 2002/0143062) in view of **Chen et al.** (US 6,267,985) and **Shudo et al.** (U.S. 5,676,146)." Specifically, the official action states that "the claimed invention, as a whole, would have been *prima facie* obvious... because every element of the invention has been collectively taught by the combined teachings of the references." Applicants respectfully disagree with this statement.

First, the official action reiterates the argument that **Lopez-Berestein et al.** teaches a method of preparing a liposome by combining N-(4-hydroxyphenyl) retinamide with a phosphatidylcholine, soybean oil, alcohol and water and that typically that liposome are deliverable in injectable compositions. However, **Lopez-Berestein et al** primarily describes and only teaches **liposomal compositions** of fenretinide for parenteral administration. **Liposomal compositions are distinct from emulsion compositions**. Liposomes are complex structures that are difficult to work with, as they suffer from difficulty of uniform

manufacture and stability, as is well documented in the general literature. Thus, the recourse of **Lopez-Berestein, et al**, to liposomal formulations of fenretinide to achieve a parenteral formulation is an implicit recognition of their failure to formulate fenretinide in a more easily manufactured and quality-controllable composition as provided by the distinctive emulsion formulation now claimed.

Further, **Lopez-Berestein et al. does not teach the use of emulsion compositions in sufficient detail to enable one of skill in the art. Lopez-Berestein et al.** devotes only two paragraphs to its discussion of emulsions, and fails to describe how to create an emulsion using the liposomal composition disclosed within the specification. In fact, although **Lopez-Berestein et al** provides no information on **how** to create a soluble composition, the specification does reveal that it is not straightforward - "[a]s is the case with may retinoids, 4-HPR is poorly soluble in water." Specification, ¶0008.

That **Lopez-Berestein et al** does not adequately enable the creation of an emulsion composition of fenretinide is further confirmed by the fact that **Lopez-Berestein et al.** requires the use of tertiarybutyl alcohol in the process of making fenretinide liposomes (column 2, paragraphs 0011 and 0013), and that tertiarybutyl alcohol is toxic to humans. Accordingly, any teachings incorporating the use of tertiarybutyl alcohol as an emulsion for parenteral administration should necessarily contain an explanation of how to neutralize the effect of the tertiarybutyl alcohol such that it no longer has a toxic effect.

Lopez-Berestein et al fails to (1) teach the use of emulsion compositions in sufficient detail to enable one of skill in the art; and (2) teach how to neutralize tertiarybutyl alcohol when making an emulsion composition as opposed to a liposomal composition. Neither **Chen et al** nor **Shudo et al** teaches or provides these missing elements.

The Official Action alleges that the disclosed invention is *prima facie* obvious. However, a finding of *prima facie* obviousness requires, among other things, that the prior art reference or combination of references must teach or suggest all of the claim recitations of the present invention. *See In re Wilson,* 165 U.S.P.Q. 494 (C.C.P.A. 1970). Where, as here, the prior art reference or combination of references fail to teach or suggest all of the claim recitations of the present invention, as discussed above, the claims may not be rejected as *prima facie* obvious. *In re Wilson,* 165 U.S.P.Q. 494 (C.C.P.A. 1970).

It is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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